REMARKS

The Official Action dated October 21, 2002 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claim 1 is amended to more clearly recite that the complex is formed in a lateral flow matrix in accordance with the preamble of claim 1, and to clarify the binding capability of the calibrator and the analyte. Claim 11 is amended for consistency, and claim 15 is amended to incorporate the Examiner's suggestion regarding the alternative language. Finally, claim 23 is amended to correspond with claim 20. It is believed that these changes do not involve any introduction of new matter and do not raise any new issues subsequent to final rejection as these amendments are in response to comments made by the Examiner in the Official Action. It is therefore further believed that entry of the amendments is in order, and entry is respectfully requested.

In the Official Action, claims 1-19 and 23 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. With respect to claim 1, the Examiner asserted that the preamble did not correlate with the body of the claim as the lateral flow matrix was not recited in the body of the claim. The Examiner also asserted that recitation of the calibrator and the analyte at lines 18 and 19 was vague and indefinite. In claim 11, the Examiner questioned how all three steps in part (d) could be done simultaneously. The Examiner asserted that claim 15 was unclear as to how (i) and (ii) could be done simultaneously, and that claim 23 contradicted independent claim 20 from which it depends.

This rejection is traversed and reconsideration is respectfully requested. More particularly, claim 1 recites that the complex is formed in a lateral flow matrix, thus corresponding with the lateral flow method recited in the preamble. Claim 1 has also been

amended to more clearly recite that the calibrator and the analyte are capable of biospecifically binding to Reactant* by equivalent binding sites. Applicants submit that it is clear to one of ordinary skill in the art therefore that the calibrator is capable of biospecifically binding to Reactant*, the analyte is capable of biospecifically binding to Reactant*, and the binding sites on Reactant* to which each of the calibrator and the analyte are capable of binding are the same. Claim 11 has been amended to clarify the flow stream recited therein, and one skilled in the art will appreciate that items i, ii and iii in step (d) are alternatives. Claim 15 has been amended as suggested by the Examiner to clarify the alternative language therein, and claim 23 has been amended to correspond with claim 20. It is therefore submitted that the claims as amended are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph, and that the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1-4, 17 and 18 were rejected under 35 U.S.C. §102(b) as being anticipated by the Robinson et al published PCT application WO 95/16914. The Examiner asserted that Robinson et al disclose a method and device for determining an analyte in a sample involving biospecific affinity reactions with the use of calibration zones in which a calibration reagent is immobilized and has biospecific affinity for the analyte of interest or a binding partner of interest. The Examiner also asserted that Robinson et al disclose that the specific binding partner can be coupled to or conjugated to the calibrator to form a complex for detection, the device may be a flow-through device, and multiple measurement zones may be employed.

In response to Applicants' arguments set forth in the previous response, the Examiner asserted that Robinson et al disclose a flow device comprising a measurement/detection zone and a reference/calibration zone through which a single fluid sample passes, and the calibrator and biospecific binding partner form complexes within the sample. The Examiner referred to Figure 4 of Robinson et al and asserted that a single flow sample flows from an application

zone towards calibrator and detection zones, whereby Robinson et al disclose a reference zone in the same flow stream as the measurement zone.

However, Applicants submit that the methods defined by claims 1-4, 17 and 18 are not anticipated by Robinson et al and are patentably distinguishable therefrom. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

As defined by claim 1, the present invention is directed to a lateral flow method for the determination of an analyte in a sample involving utilizing biospecific affinity reactions. The method comprises forming a complex in a flow matrix, the complex comprising Reactant I --- Analyte' --- Reactant* wherein Reactant* and Reactant I exhibit biospecific affinity to the analyte, Reactant* is analytically detectable, and Analyte' is the analyte or an analyte-related reactant. The method further comprises determining a detectable signal from Reactant* in the complex (sample value), and obtaining the amount of analyte in the sample by comparing the sample value with one or more calibrator values, each of which corresponds to a standard amount of analyte. Before determination of the calibrator value, either calibrator or a binder for the calibrator has been bound to a matrix and the calibrator is added or calibrator predeposited in the matrix is released at the determination of calibrator value. The matrix is insoluble in the liquid medium in which binding of Reactant* to the calibrator occurs. The calibrator and the analyte are capable of biospecifically binding to Reactant* by equivalent binding sites, and one or more calibrator zones comprising calibrator or binder for the calibrator are located in the same process flow as Reactant I in a detection zone.

The methods according to the present invention provide improvements in analyte determinations employing calibrators. Particularly, the present methods enable compensation for the differences that may exist between calibrator and sample solution and between runs performed at different times and/or different places. These advantages are obtained by the defined methods of claim 1, employing Reactant* which binds to either analyte or calibrator,

and forming the complex in the flow matrix and wherein the calibrator zone or zones are located in the same process flow as the detection zone for measuring analyte.

Robinson et al disclose a sensor device for sandwich assay, for example a capillary fill device (CFD). In Figure 4 referenced by the Examiner, Robinson et al show a CFD formed of two opposed plates, one supplying a test zone of capture antibody (Y) and four reference zones of capture antibody (Y), and the other plate supplying labeled second antibody (L) to the test zone and labeled second antibody (L) and antigen dosed into the device (□) to the reference zones. The Robinson et al method begins with an incubation step, without flow, in which antigen and antibody are released, i.e., solubilized, after sample filling. See, for example, page 4, line 26 and page 7, lines 23-31. The reference zones are used to alert the user that the concentration of analyte present in the sample is greater than a high-dose hook concentration whereby the user can then dilute a sample for further measurement.

However, Applicants find no teaching or suggestion by Robinson et al of a lateral flow method as defined by claim 1 which comprises forming a complex in a flow matrix, particularly wherein the complex comprises Reactant I --- Analyte' --- Reactant*, wherein Reactant* and Reactant I exhibit biospecific affinity to the analyte, wherein a calibrator and an analyte are capable of biospecifically binding to an analytically detectable reactant (Reactant*) via equivalent binding sites and wherein a calibrator zone comprising calibrator or binder is located in the same process flow as Reactant I in a detection zone. Rather, in the Robinson et al system, both the labeled second antibody (L) and the antigen dosed into the device (□) are preloaded and released after sample filling, during incubation, but no process flow of sample and reagent takes place. Additionally, Applicants find no teaching or suggestion by Robinson et al relating to the advantages provided by the presently claimed methods wherein the complex is formed in a flow matrix, particularly, that the calibration is relevant to a particular sample and the conditions under which the sample is processed

through the process flow stream, and that compensation is enabled for differences between calibrator and sample solution as well as between runs performed at different times and/or at different places.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q.2d 1949 (Fed Cir. 1999). In view of these deficiencies in the teachings of Robinson et al, Robinson et al do not anticipate claims 1-4, 17 and 18 under 35 U.S.C. §102. It is therefore submitted that the rejection has been overcome. Reconsideration is respectfully requested.

Claims 20-25 and 27-37 were rejected under 35 U.S.C. §102(b) as being anticipated by the Rylatt et al published PCT application WO 97/09620. The Examiner referred to Figs. 2, 5 and 8 and asserted that Rylatt et al disclose a lateral flow permeable medium or matrix, and a calibration zone comprising a calibration agent receptor immobilized to the matrix, wherein labeled calibration agent is transported through the calibrator zone and applied in an application zone upstream of the calibrator zone.

However, Applicants submit that the devices defined by claims 20-25 and 27-37 are not anticipated by Rylatt et al and are patentably distinguishable therefrom. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, according to claim 20, the invention is directed to a device for transforming measured signal values of a complexed, analytically detectable reactant (Reactant*) to real amounts of analyte in a sample, in connection with performing an analysis method which utilizes biospecific affinity reactions for the determination of the amount of analyte in a sample, to form complexes comprising Reactant* in an amount which is related to the amount of analyte in the sample. The device exhibits a flow matrix in which there is an area of process flow for the transport of Reactant*. In said area are (i) one or more calibrator

zones (CZ) comprising a calibrator, or binder for the calibrator, which is firmly anchored to the matrix, the amounts of calibrator or calibrator binder, respectively, being different for at least two calibrator zones when at least two calibrator zones are present, and the calibrator exhibiting binding sites to which Reactant* binds, when Reactant* is transported through a calibrator zone, (ii) an application zone for Reactant* ($A_{R^*}Z$) upstream of said one or more calibrator zones, and (iii) one or more detection zones (DZ) downstream of said one or more calibrator zones. Thus, in the devices of claim 20, the zone ($A_{R^*}Z$) for application of Reactant*, which binds to both calibrator and sample analyte, is upstream of the one or more calibrator zones, and the one or more detection zones (DZ) are downstream of the one or more calibrator zones.

Rylatt et al disclose a device for determination of an analyte in a sample. With reference to Fig. 2 cited by the Examiner, the Rylatt et al device includes a test zone 204 arranged between calibration zones 210 and 211. Thus, the detection or test zone is not downstream of the one or more calibration zones, but interspersed therein. Moreover, Applicants find no teaching or suggestion by Rylatt et al of a device employing Reactant* as presently claimed, binding to both calibrator and analyte. Rather, as shown in Fig. 2 of Rylatt et al, the procedure of Rylatt et al employs an analyte detection agent 208 for binding in the test zone and a separate calibration agent 209 for binding in the calibration zone. Further, the procedure described in Fig. 2 of Rylatt et al employs a separate support element for diffusibly attaching the analyte detection agent 208 and the calibration agent 209, and Applicants find no teaching or suggestion by Rylatt et al as to where such elements would be provided in the flow matrix 207. In view of these deficiencies in the teachings of Rylatt et al, Rylatt et al do not disclose each element of the claims and therefore do not anticipate claims 20-25 and 27-37 under 35 U.S.C. §102. It is therefore submitted that the rejection has been overcome. Reconsideration is respectfully requested.

Claims 6 and 11-16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Robinson et al in view of Rylatt et al. The Examiner asserted it would have been obvious to incorporate deposition and transportation of Reactant* as taught by Rylatt et al in the method of Robinson et al.

However, Applicants submit that the methods defined by claims 6 and 11-16 are nonobvious over and patentably distinguishable from Robinson et al in view of Rylatt et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Claims 6 and 11-16 depend from claim 1. The deficiencies of Robinson et al with respect to claim 1 are discussed in detail above and are not resolved by Rylatt et al. More particularly, Applicants find no teaching or suggestion by Robinson et al of a lateral flow method as defined by claim 1 which comprises forming a complex in a flow matrix, particularly wherein the complex comprises Reactant I --- Analyte' --- Reactant*, wherein Reactant* and Reactant I exhibit biospecific affinity to the analyte, wherein a calibrator and an analyte are capable of biospecifically binding to an analytically detectable reactant (Reactant*) via equivalent binding sites and wherein a calibrator zone comprising calibrator or binder is located in the same process flow as Reactant I in a detection zone. Moreover, as noted above, Applicants find no teaching or suggestion by Rylatt et al for employing Reactant* as presently claimed, binding to both calibrator and analyte. Rather, as shown in Fig. 2 of Rylatt et al, the procedure of Rylatt et al employs an analyte detection agent 208 for binding in the test zone and a separate calibration agent 209 for binding in the calibration zone. Thus, the cited combination does not render obvious the method of claim 1 or claims 6 and 11-16 dependent thereon.

Additionally, claim 6 requires transport of Reactant* through the calibrator zones, while claims 11-16 require the use of an application zone for Reactant*, $A_{R^*}Z$, which is located upstream of the calibration zones and the detection zones. In contrast, Robinson et al

predeposit labeled antibody and dosed antigen at the reference and test zones. Applicants find no teaching or suggestion for modifying the device of Robinson et al to include any of the features of Rylatt et al. In fact, flow of the labeled second antibody (L) and the antigen dosed into the device (□) through the CFD disclosed by Robinson et al would disadvantageously influence the operation of the reference zones shown in Fig. 4 of Robinson et al.

Thus, the methods defined by claims 6 and 11-16 are nonobvious over and patentably distinguishable from Robinson et al in view of Rylatt et al, whereby the rejection has been overcome. Reconsideration is respectfully requested.

Claim 19 was rejected under 35 U.S.C. §103(a) as being unpatentable over Robinson et al in view of the Self U.S. Patent No. 4,446,231. The Examiner relied on Self as disclosing that immunoassays are used for detection and/or determination of autoimmune diseases.

However, Applicants submit that the methods defined by claim 19 are nonobvious over and patentably distinguishable from the teachings of Robinson et al and Self. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The deficiencies of Robinson et al with respect to claim 1, on which claim 19 depends, are discussed in detail above. Self does not resolve these deficiencies. That is, Self discloses an immunoassay employing an enzyme label which converts a precursor into a cycling factor which in turn is interconverted in a cycling detection system. Applicants find no teaching or suggestion by Self relating to a lateral flow method wherein a complex is formed in a lateral flow matrix as defined in present claim 1 and employing one or more calibration zones, particularly in the same process flow as a detection zone.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). In view of the failure of Robinson et al and Self to

teach a lateral flow method as claimed, the combination of Robinson et al and Self does not enable one of ordinary skill in the art to conduct the method of claim 1 and therefore does not render claim 1, or claim 19 dependent thereon, obvious. It is therefore submitted that the rejection of claim 19 under 35 U.S.C. §103 based on Robinson et al and Self has been overcome. Reconsideration is respectfully requested.

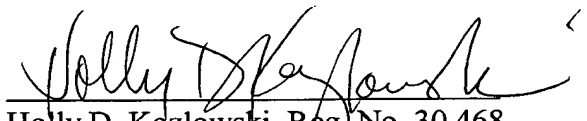
Claim 26 was rejected under 35 U.S.C. §103(a) as being unpatentable over Rylatt et al in view of the Weng et al U.S. Patent No. 4,740,468. The Examiner relied on Weng et al as disclosing the use of a specific binding partner that is biospecific to a second binding partner which in turn is specific for an analyte. The Examiner asserted it would have been obvious to incorporate an immobilized specific binding partner as taught by Weng et al in the device of Rylatt et al.

However, Applicants submit that the device defined by claim 26 is nonobvious over and patentably distinguishable from the combination of Rylatt et al and Weng et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The deficiencies of Rylatt et al have been discussed above with respect to claim 20, on which claim 26 depends, and are not resolved by Weng et al. That is, Weng et al disclose a method and device for determining the presence of an analyte in a sample suspected of containing the analyte. Applicants find no teaching or suggestion by Weng et al for modifying the device of Rylatt et al in accordance with the device as recited in claim 20, wherein the detection or test zone is downstream of the one or more calibration zones, a Reactant* as presently claimed, binding to both calibrator and analyte, is employed, and where such Reactant* is arranged in the flow matrix. Thus, Weng et al do not resolve the deficiencies of Robinson et al. It is therefore submitted that the rejection under 35 U.S.C. §103 based on these references has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §§ 102, 103 and 112, second paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested. In the event that the present application is not in condition for allowance, entry of the present Amendment for purposes of appeal is requested.

Respectfully submitted,



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VERSION WITH MARKINGS SHOWING CHANGES MADE

In the Claims:

Please amend claims 1, 11, 15 and 23 to read as follows:

1. (Third Amendment) A lateral flow method for the determination of an analyte in a sample involving utilizing biospecific affinity reactions, and comprising the following steps:

i. forming a complex in a lateral flow matrix, the complex comprising:

Reactant I---Analyte'---Reactant*, where

a. Reactant* and Reactant I exhibit biospecific affinity to the analyte,

b. Reactant* is analytically detectable,

c. Analyte' is the analyte or an analyte-related reactant, and subsequently

ii. determining a detectable signal from Reactant* in the complex (sample value), and

iii. obtaining the amount of analyte in the sample by comparing the sample value with one or more calibrator values, each of which corresponds to a standard amount of analyte,

wherein A) before determination of the calibrator value, either (i) calibrator or (ii) a binder for the calibrator has been bound to a matrix, and when a binder for the calibrator has been bound to the matrix, calibrator is added or calibrator predeposited in the matrix is released at the determination of calibrator value, and wherein the matrix is insoluble in the liquid medium in which binding of Reactant* to the calibrator occurs, B) the calibrator and the analyte [have the ability to] are capable of biospecifically [bind] binding to Reactant* [via] by equivalent binding sites, and C) one or more calibrator zones CZ comprising

calibrator or binder for the calibrator are located in a single process flow stream with Reactant I in a detection zone (DZ).

11. (Third Amendment) The method according to claim 1, wherein along a single matrix is [a] the flow matrix, and wherein along a single process flow stream, there are

a. one or more calibrator zones (CZ), each of which exhibits a matrix calibrator or a matrix calibrator binder,

b. one or more detection zones (DZ), none of which coincides with any calibrator zone, and in which a Capturer is firmly anchored and is either Reactant I or a biospecific affinity reactant, which directly or indirectly binds Reactant I biospecifically,

c. an application zone for Reactant*, $A_{R^*}Z$, which is located upstream of said CZ and DZ and to which Reactant* is optionally predeposited, and

d. an application zone for sample (A_SZ) which is located

i. upstream of or coinciding with a detection zone,

ii. downstream or upstream of or coinciding with $A_{R^*}Z$ ($A_SZ/A_{R^*}Z$), or

iii. upstream of, downstream of or coinciding with a calibrator zone,

[wherein the zone of application of sample (A_SZ) is located upstream of both detection and calibrator zones, and] wherein Reactant* is added to $A_{R^*}Z$ if Reactant* is not predeposited, or buffer is added to $A_{R^*}Z$ if Reactant* is predeposited, and sample is added to A_SZ, optionally premixed with Reactant* if A_SZ and $A_{R^*}Z$ coincide, such that analyte and Reactant* reach DZ at the same time, or such that analyte reaches DZ before Reactant*.

15. (Third Amendment) The method according to claim 11, wherein

a. A_SZ is (i) common to $A_{R^*}Z$, forming a common zone (= $A_SZ/A_{R^*}Z$) or (ii) is located upstream of $A_{R^*}Z$, and

b. for alternative (i) sample is premixed with Reactant* before it is added to the common zone $A_SZ/A_{R*}Z$, or sample is added to the common zone $A_SZ/A_{R*}Z$ containing predeposited Reactant*, [and] or for alternative (ii), sample is added to A_SZ, which is located upstream of $A_{R*}Z$ which in turn comprises predeposited Reactant*.

23. (Twice Amended) The device according to claim 20, wherein the process flow comprises a detection zone (DZ) which is located downstream of [or coinciding with] $A_{R*}Z$ and comprises a firmly anchored Capturer via which Reactant* can bind to DZ, and a zone of application of sample (A_SZ) which is located upstream of or coincides with said DZ.

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